

WHAT IS CLAIMED IS:

1. An isolated or purified antigenic polypeptide comprising the amino acid sequence of factor VIII or a fragment thereof.

2. An isolated or purified antigenic polypeptide comprising a factor VIII polypeptide which lacks the following fragments: alanine 322 - serine 750, leucine 1655 - arginine 1689, lysine 1694 - proline 1782 and possibly the fragment aspartic acid 2170 - tyrosine 2332.

3. The polypeptide according to Claim 1 or Claim 2, wherein said polypeptide exhibits an immunoaffinity for the receptors of T and/or B lymphocytes.

4. An isolated or purified antigenic fragment of factor VIII, wherein said fragment is selected from the group consisting of the polypeptide sequences A1, A2, A3 or C of factor VIII or a portion thereof.

5. The antigenic fragment of Claim 4 wherein said fragment is selected from the group consisting of the sequence fragment arginine 1649 to arginine 2031 inclusive, the sequence fragment threonine 1739 to aspartic acid 1831 inclusive, the sequence fragment arginine 1803 to arginine 1917 inclusive and any of the preceding fragments wherein at least one amino acid has been deleted.

6. An isolated or purified polypeptide comprising an epitope of factor VIII, wherein said epitope is selected from the group consisting of:

(a) the epitope arginine 1648 to tyrosine 1664 inclusive, defined by the following sequence:

SEQ ID NO: 1:

Arg Asp Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln Glu Glu Ile Asp Tyr ,

(b) the epitope of (a) wherein one or more amino acids of the tetrapeptide Arg-Asp-Ile-Thr or one or two of the last amino acids of the peptide Asp-Tyr;

(c) the epitope aspartic acid 1681 to arginine 1696 inclusive, defined by the following sequence:

SEQ ID NO: 2:

Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys Lys Thr Arg ,

(d) the epitope of (c) wherein one or more amino acids of the epitope Asp-Glu-Asp-Glu are deleted;

(e) the epitope threonine 1739 to tyrosine 1748 inclusive, defined by the following sequence:

SEQ ID NO: 3:

Thr Asp Gly Ser Phe Thr Gln Pro Leu Tyr;

5 (f) the epitope asparagine 1777 to phenylalanine 1785 inclusive, defined by the following sequence:

SEQ ID NO: 4:

Asn Gln Ala Ser Arg Pro Tyr Ser Phe ;

10 (g) the epitope of (f) wherein one or two amino acids of the terminal dipeptide Ser-Phe or the tetrapeptide Pro-Tyr-Ser-Phe are deleted;

(h) the epitope glutamic acid 1794 to tyrosine 1815 inclusive, defined by the following sequence:

SEQ ID NO: 5:

Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg Lys Asn Phe Val Lys Pro

15 Asn Glu Thr Lys Thr Tyr ;

(i) the epitope of (h) wherein one or more amino acids from the first tripeptide Glu-Asp-Gln or the first nonapeptide Glu-Asp-Gln-Arg-Gln-Gly-Ala-Glu-Pro are deleted;

20 (j) the epitope methionine 1823 to aspartic acid 1831, defined by the following sequence:

SEQ ID NO: 6:

Met Ala Pro Thr Lys Asp Glu Phe Asp;

(k) the epitope glutamic acid 1885 to phenylalanine 1891 inclusive, defined by the following sequence:

25 SEQ ID NO: 7:

Glu Thr Lys Ser Trp Tyr Phe ;

(l) the epitope glutamic acid 1885 to alanine 1901 inclusive, defined by the following sequence:

SEQ ID NO: 8:

30 Glu Thr Lys Ser Trp Phe Thr Glu Asn Met Glu Arg Asn Cys Arg Ala ;

(m) the epitope of (l) wherein one or more amino acids from the heptapeptide

Gly-Thr-Lys-Ser-Trp-Phe-Thr or from the tripeptide Cys-Arg-Ala are deleted;

(n) the epitope aspartic acid 1909 to arginine 1917 inclusive, defined by the following sequence:

SEQ ID NO: 9:

5 Asp Pro Thr Phe Lys Glu Asn Tyr Arg;

(o) the epitope comprised between serine 2018 and histidine 2031 inclusive, defined by the following sequence:

SEQ ID NO: 10:

Ser Asn Lys Cys Gln Thr Pro Leu Gly Met Ala Ser Gly His; and

10 (p) any of the preceding epitopes (a) to (o) wherein at least one amino acid has been deleted.

15 7. The antigenic fragment of Claim 4, wherein said fragment is selected from the group consisting of alanine 108 to methionine 355 inclusive, alanine 108 to alanine 227 inclusive and any of the preceding fragments wherein at least one amino acid has been deleted.

8. An isolated or purified polypeptide comprising an epitope of factor VIII, wherein said epitope is selected from the group consisting of:

(a) the epitope alanine 108 to valine 128 inclusive, defined by the following sequence:

20 SEQ ID NO: 11:

Ala Ser Glu Gly Ala Glu Tyr Asp Asp Gln Thr Ser Gln Arg Glu Lys
Glu Asp Asp Lys Val;

(b) the epitope of (a) wherein the terminal amino acids alanine and/or valine are deleted;

25 (c) the epitope glutamic acid 181 to leucine 192 inclusive, defined by the following sequence:

SEQ ID NO: 12:

Glu Gly Ser Leu Ala Lys Glu Lys Thr Gln Thr Leu;

30 (d) the epitope of (a) wherein one or two amino acids of the terminal dipeptide Thr-Leu are deleted;

(e) the epitope aspartic acid 203 to alanine 227 inclusive, defined by the following sequence:

SEQ ID NO: 13:

Asp Glu Gly Lys Ser Trp His Ser Glu Thr Lys Asn Ser Leu Met Gln

5 Asp Arg Asp Ala Ala Ser Ala Arg Ala;

(f) the epitope of (e) wherein one or more amino acids of the nonapeptide Asp-Arg-Asp-Ala-Ala-Ser-Ala-Arg-Ala are deleted;

(g) the epitope aspartic acid 327 to methionine 355 inclusive, defined by the following sequence:

10 SEQ ID NO: 14:

Asp Ser Cys Pro Glu Glu Pro Gln Leu Arg Met Lys Asn Asn Glu Glu

Ala Glu Asp Tyr Asp Asp Asp Leu Thr Asp Ser Glu Met;

(h) the epitope of (g) wherein one or more amino acids of the dipeptide Asp-Ser or the octapeptide Asp-Asp-Leu-Thr-Asp-Ser-Glu-Met are deleted; and

15 (i) any of the preceding epitopes (a) to (h) wherein at least one amino acid has been deleted.

9. The antigenic fragment of Claim 4, wherein said fragment is selected from the group consisting of aspartic acid 403 to aspartic acid 725 inclusive, histidine 693 to aspartic acid 725 inclusive and any of the preceding fragments wherein at least one amino acid has been deleted..

20 10. An isolated or purified polypeptide comprising an epitope of factor VIII, wherein said epitope is selected from the group consisting of:

(a) the epitope aspartic acid 403 to lysine 425 inclusive, defined by the following sequence:

25 SEQ ID NO: 15:

Asp Asp Arg Ser Tyr Lys Ser Gln Tyr Leu Asn Asn Gly Pro Gln Arg

Ile Gly Arg Lys Tyr Lys Lys;

(b) the epitope of (a) wherein one or more amino acids of the tetrapeptide Asp-Asp-Arg-Ser are deleted;

30 (c) the epitope valine 517 to arginine 527 inclusive, defined by the following sequence:

SEQ ID NO: 16:

Val Glu Asp Gly Pro Thr Lys Ser Asp Pro Arg;

(d) the epitope of (c) wherein one or the two amino acids of the dipeptide Pro-Arg are deleted;

5 (e) the epitope tyrosine 555 to glutamine 565 inclusive defined by the following sequence:

SEQ ID NO: 17:

Tyr Lys Glu Ser Val Asp Gly Arg Gly Asn Gln;

10 (f) the epitope histidine 693 to glycine 701 inclusive, defined by the following sequence:

SEQ ID NO: 18

His Asn Ser Asp Phe Arg Asn Arg Gly;

(g) the epitope serine 710 to aspartic acid 725 inclusive, defined by the following sequence:

15 SEQ ID NO: 19

Ser Cys Asp Lys Asn Thr Gly Asp Tyr Try Gly Asp Ser Tyr Glu Asp;

(h) the epitope leucine 730 to serine 741 inclusive, defined by the following sequence:

SEQ ID NO: 20:

20 Leu Leu Ser Lys Asn Asn Ala Ile Glu Pro Arg Ser;

(i) the epitope of (h) wherein the terminal amino acid serine and/or the first amino acid leucine are deleted;

(j) the epitope serine 817 to serine 830 inclusive, defined by the following sequence:

25 SEQ ID NO: 21:

Ser Asp Asp Pro Ser Gly Ala Ile Asp Ser Asn Asn Ser; and

(k) any of the preceding epitopes (a) to (j) wherein at least one amino acid has been deleted.

30 11. The antigenic fragment of Claim 4, wherein said fragment is selected from the group consisting of lysine 2085 to isoleucine 2251 inclusive, leucine 2273 to tyrosine 2332 inclusive, lysine 2085 to glycine 2121 inclusive, serine 2182 to leucine

2251 inclusive and any of the preceding fragments wherein at least one amino acid has been deleted.

12. An isolated or purified polypeptide comprising an epitope of factor VIII, wherein said epitope is selected from the group consisting of:

5 (a) the epitope isoleucine 2081 to serine 2095 inclusive, defined by the following sequence:

SEQ ID NO: 22:

Ile His Gly Ile Lys Thr Gln Gly Ala Arg Gln Lys Phe Ser Ser;

(b) the epitope of (a) wherein one or more amino acids of the tetrapeptide Ile-
10 His-Gly-Ile are deleted;

(c) the epitope tyrosine 2105 to glycine 2121 inclusive, defined by the following sequence:

SEQ ID NO: 23:

Tyr Ser Leu Asp Gly Lys Lys Trp Gln Thr Tyr Arg Gly Asn Ser Thr Gly;

15 (d) the epitope of (c) wherein one or more amino acids of the tripeptide Tyr-Ser-Leu are deleted;

(e) the epitope asparagine acid 2128 to asparagine acid 2138 inclusive, defined by the following sequence:

SEQ ID NO: 24:

20 Asn Val Asp Ser Ser Gly Ile Lys His Asn;

(f) the epitope histidine 2152 to arginine 2163 inclusive, defined by the following sequence:

SEQ ID NO: 25:

His Pro Thr His Tyr Ser Ile Arg Ser Thr Leu Arg;

25 (g) the epitope serine 2181 to asparagine acid 2198 inclusive, defined by the following sequence:

SEQ ID NO: 26:

Ser Lys Ala Ile Ser Asp Ala Gln Ile Thr Ala Ser Ser Tyr Phe Thr Asn;

(h) the epitope of (g) wherein one or more amino acids of the first dipeptide Ser-
30 Tyr or one or more amino acids from the terminal tripeptide Phe-Thr-Asn are deleted;

(i) the epitope serine 2204 to glutamine 2222 inclusive, defined by the following sequence:

SEQ ID NO: 27:

Ser Pro Ser Lys Ala Arg Leu His Leu Gln Gly Arg Ser Asn Ala Trp

5 Arg Pro Gln ;

(j) the epitope glutamine 2235 to leucine 2251 inclusive, defined by the following sequence:

SEQ ID NO: 28:

Gln Lys Thr Met Lys Val Thr Gly Val Thr Thr Gln Gly Val Lys Ser Leu;

10 (k) the epitope of (j) wherein one or two amino acids of the terminal dipeptide Ser-Leu or one or more amino acids of the tetrapeptide Val-Lys-Ser-Leu are deleted;

(l) the epitope glycine 2242 to leucine 2251 inclusive, defined by the following sequence:

SEQ ID NO: 29:

15 Gly Val Thr Thr Gln Gly Val Lys Ser Leu;

(m) the epitope of (l) wherein one or two amino acids of the terminal dipeptide Ser-Leu are deleted;

- (n) the epitope isoleucine 2262 to glutamine 2270 inclusive, defined by the following sequence:

20 SEQ ID NO: 30:

Ile Ser Ser Ser Gln Asp Gly His Gln;

(o) the epitope leucine 2273 to serine 2289 inclusive, defined by the following sequence:

SEQ ID NO: 31:

25 Leu Phe Phe Gln Asn Gly Lys Val Lys Val Phe Gln Gly Asn Gln Asp Ser;

(p) the epitope proline 2292 to tyrosine 2305 inclusive, defined by the following sequence:

SEQ ID NO: 32:

Pro Val Val Asn Ser Leu Asp Pro Pro Leu Leu Thr Arg Tyr;

30 (q) the epitope of (p) wherein one or more amino acids of the terminal tripeptide Thr-Arg-Tyr are deleted;

(r) the epitope glutamic acid 2322 to tyrosine 2332 inclusive, defined by the following sequence:

SEQ ID NO: 33:

Glu Val Leu Gly Cys Glu Ala Gln Asp Leu Tyr; and

5 (s) any of the preceding epitopes (a) to (r) wherein at least one amino acid has been deleted.

13. A purified or isolated conformational epitope, which contains at least two different epitopes according to any one of claims 7, 9 and 11 and any of the preceding epitopes wherein at least one amino acid has been deleted.

10 14. A pool of more than three fragments or epitopes according to any of the preceding claims 5 to 12.

15. A complex comprising a carrier protein or a carrier peptide linked to an antigenic fragment or epitope from factor VIII.

15 16. An inhibitor of factor VIII, which exhibits an immunoaffinity with an element selected from the group consisting of factor VIII, an antigenic fragment thereof, an epitope therefrom, and a complex comprising any of the foregoing polypeptides.

17. The inhibitor according to Claim 16, wherein said inhibitor is an anti-factor VIII antibody or antibody fragment.

20 18. An anti-inhibitor directed against the inhibitor of factor VIII according to Claim 16 or 17.

19. An anti-inhibitor according to Claim 18, wherein said anti-inhibitor is an anti-anti-factor VIII idiotype antibody or antibody fragment.

25 20. A pharmaceutical composition comprising an adequate pharmaceutical carrier and at least one element selected from the group consisting of factor VIII, an antigenic fragment thereof, an epitope therefrom, a complex comprising any of the foregoing polypeptides, an inhibitor of any of the foregoing polypeptides and an anti-inhibitor of any of the foregoing polypeptides.

30 21. A diagnostic and/or purification device, which comprises at least one element selected from the group consisting of factor VIII, an antigenic fragment thereof, an epitope therefrom, a complex comprising any of the foregoing polypeptides, an inhibitor

of any of the foregoing polypeptides and an anti-inhibitor of any of the foregoing polypeptides.

22. The device according to Claim 21, wherein said device is a diagnostic kit.

23. The device according to Claim 21, wherein said device is a chromatography column or filter.

24. A method for a therapeutic treatment and/or prevention of an immune disorder in mammal, wherein the pharmaceutical composition according to Claim 20 is administered to a mammal presently or potentially having said immune disorder, in an amount effective to treat and/or prevent said immune disorder.

25. A method for a therapeutic treatment and/or prevention of an immune disorder in a mammal, wherein a physiological fluid such as serum obtained from said mammal is put into the chromatography column of Claim 23 in order to allow binding of the inhibitors of factor VIII present in said serum to an element selected from the group consisting of factor VIII, an antigenic fragment thereof, an epitope therefrom, and a complex comprising any of the foregoing polypeptides, wherein the physiological liquid is eluted from said chromatography column and the physiological liquid from which the inhibitors of factor VIII have been removed is reinjected to the patient.

26. The therapeutic treatment and/or prevention method according to Claim 24 or 25, wherein the immune disorder is induced by an element selected from the group consisting of inhibitors of factor VIII, inhibitors of the binding of factor VIII to the von Willebrand factor, inhibitors of the binding of factor VIII to the factor IX, inhibitors of the binding of factor VIII to the factor X and inhibitors of the binding of factor VIII to membrane phospholipids.

27. A process for identifying and obtaining inhibitors and/or anti-inhibitors comprising:

attaching an element selected from the group consisting of factor VIII, an antigenic fragment thereof, an epitope therefrom, a complex comprising any of the foregoing polypeptides, an inhibitor of any of the foregoing polypeptides and an anti-inhibitor of any of the foregoing polypeptides to a solid support of a chromatography column;

passing a physiological fluid from a patient containing inhibitors of factor VIII through said chromatography column;

eluting said column; and

5 collecting the fractions containing inhibitors of factor VIII which have exhibited an immunoaffinity with said element.

28. The process according to Claim 27, further comprising the steps of:

attaching the collected inhibitors of factor VIII to the solid support of a chromatography column;

10 passing a physiological fluid from a patient containing anti-inhibitors of factor VIII through said chromatography column;

eluting said column; and

collecting the fractions containing anti-inhibitors of factor VIII which have exhibited an immunoaffinity with said inhibitors of factor VIII.

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